REMARKS

Claims 1 to 4, and 6 to 13, and 16 to 21 are in the application. Claims 6, 7 and 16 have been amended. Claims 17 to 21 have been added. Support for the newly added claims and the amendments to Claim 6 and 7 lie in the claims as originally filed, or in the specification on page 9, lines 31 -32; and page 10, lines 1 to 20. The amendment to Claim 16 corrects a grammatical error. No new matter is believed added.

The Examiner comments the Claim 6 is "objected to for improper grammar. After the words "binding of acetylcholine to" the word "a" should be replaced with "an". Applicants respectfully traverse this objection. The indefinite article, "a" or "an" is to be used the first time an element is used in a claim. While "an" may be more proper, grammatically, it is believed the permissive use of the article "a" is acceptable. However, in order to advance prosecution on the merits the claim has been amended as suggested by the Examiner.

Rejection under 35 USC § 103

Claims 1 to 4 are rejected to under 35 USC § 103(a) as being unpatentable over Zirkle et al. (US Patent 2,800,478 ('478)) or Zirkle et al., J. Med. Chem. (1962) in view of Gillett et al., European Respiratory Journal (1988) and Sieger et al., US Patent 6,608,055 ('055). Applicant respectfully traverses this rejection.

With respect to the Examiner's comments on Applicants arguments, it is not that one Zirkle reference is better than another it is that the USPTO is required to be clear and concise in their rejections of the claims over cited prior art. The Examiner is not allowed to change midstream in an office action and use a different piece of prior art, albeit one which has the same inventor without providing the requisite time and ability of Applicants to argue accordingly and if necessary to make claim amendments. This the Examiner did not do properly. In one office action the rejection was over a Zirkle et al., J. Med. Pharm. Chem. Publication from 1962. In the second the rejection was over a Zirkle et al. US patent, US 2,800,478 which is a <u>different citation and prior art reference</u>. Consequently, regardless of how close the art may appear to be it is an improper final rejection that necessitated the filing of this continuation application.

In fact, the Examiner has now made the instant rejection over both of these pieces of prior art which further substantiates Applicants argument that the finality of the prior office action was in error.

More importantly in the present rejection, while the Examiner cites a European Respiratory Journal, Abstract only on the PTO 892 form, the USPTO has failed to include a copy of this article as required by the Manuel, see §707.05(a) below:

> **707.05(a) Copies of Cited References [R-3]**
>
> Copies of cited >foreign patent documents and non-patent literature< references (except as noted below) are automatically furnished without charge to applicant together with the Office action in which they are cited. Copies of the cited references are also placed in the application file for use by the examiner during the prosecution.>Copies of U.S. patents and U.S. patent application publications are not provided in paper to applicants and are not placed in the application file.<

Consequently, the rejection is improper for failure of the USPTO to follow its own requirements.

US Patent 2,800,478 is stated to teach:

"the compounds of the current invention as a solid manipulated in air and thus inherently containing the air (the composition would be composed of particles of the compound in a composition with air and such a composition would inhalable)".

Applicants request the Examiner to point out where in the '478 patent the "solids" are "manipulated in the air and thus inherently contain the air". Simply because a compound exists as a solid does not render that compound as a) a "composition", as that requires a suitable excipient with the compound and b) that excipient may not be suitable for use as an inhaled composition. The US Patent 2,800,478 does NOT describe a dry powder composition of pharmaceutical quality suitable for inhalation therapy via the mouth. It should also be noted that oral administration of a composition may include carriers or excipients that are unacceptable for topical administration of the lung tissue by dry powder inhalation.

The Examiner points out that a compound having Registry # 106655-97-4 is taught in Col. 9 of US Patent 2,800,478 (See Office Action, page 5, last ¶, and page 6), and that this compound "is synthesized and evaluated for its anticholinergic activity". From this the Examiner then comments that "Clearly solid compounds, ethanol or ethanol ether solutions of these compounds can be inhaled".

As commented by Applicants in their January 2008 response which is incorporated by reference herein, there is no solely ethanolic solution described for this compound in the '478 patent. It is an ethanol/ether re-crystallization mixture. Applicants challenge the Examiner's assertion that an ethanol/ether mixture would be suitable for use as an inhalable liquid composition, and request supporting documentation of such.

The claims herein are directed to a dry powder inhalation composition, not a liquid composition such as a solution or suspension, for inhalation. The devices claimed in claims 9 and 10 and newly added claims 18 to 20 are specific to "powder" compositions for use therein.

The Examiner then discusses in the Office Action, the Zirkle et al. Med. Chem. article in some detail. However, on page 8 of the Office action, the Examiner concludes, without any apparent reference specifically that:

"Furthermore it is apparent that the reference inherently discloses solid material (which is inhalable and exists as a composition with air at atmospheric pressure".

Applicants believe that the Examiner is misinformed as to what constitutes a "composition". Composition of matter claims are combination claims. The compound is claimed in combination with another substance or material. Air has not been considered a substance for the purposes of composition claims.

More importantly it should be noted, is that neither the Zirkle et al., Med Chem. article nor the '478 patent discloses, or discuss in any manner a combination of the compounds disclosed therein as a pharmaceutical composition. It does not teach how one would formulate the compounds for delivery to a human by any accepted route of administration, e.g. orally, topically, intravenously, intramuscularly or inhaled.

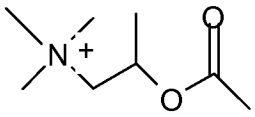
The Examiner points to a footnote on page 353 of the Zirkle paper that states the data was supplied by Mr. Edward Macko. The relevance of this is not seen. The brief abstract of the paper on page 341 indicates quite clearly that some of the compounds described in the paper have been tested for "*in vitro* cholinolytic activity"

which "equals or exceeds that of atropine". Table IV referenced on page 352 contains no biological data. The prior table, on page 351 does contain biological data for 8 of the 25 compounds listed therein. The compound on page 352 is not one of those with data shown for it.

The Examiner is correct that this paper is "not clear what tissues were involved", and more so it is quite clear that the paper does NOT discuss the manner in which the compounds were tested in vitro. The testing of the compounds for activity is NOT an *in vivo* use of those compounds, nor is it a disclosure of a particular route of administration, e.g. inhalation by mouth to a human.

The Examiner cites to an abstract of Gillett et. al., for the purposes of teaching an "inhaled formulation". In the Gillett article, methacholine chloride is adminsitered by an aerosol. Methacholine is a synthetic choline ester that acts as a non-selective muscarinic receptor agonist in the parasympathetic nervous system. The primary clinical use of methacholine is to diagnose bronchial hyperreactivity, which occurs in asthma. This is accomplished through the methacholine challenge test.

Methacholine is 2-acetyloxypropyl-trimethyl-azanium, and has a structure of:



The Gillett abstract does not indicate how either the methacholine or the atropine was formulated. The abstract merely says that six asthmatic subjects were given increasing concentrations of methacholine aerosol which could be powder or liquid. The abstract also states that the subjects were premedicated with 0.9% sodium chloride (saline), or inhaled atropine at 4 different doses, or intravenous atropine. No formulation details are provided.

The Examiner comments that "clearly the preparation of an inhalable formulation of these compounds is trivial undertaking as per US patent 6,608,055 (see columns 9 and 10) it would be obvious to prepare a different formulation (a dry powder with additives) and test them as anticholinergic as per the teaching of Zirkle". (See Office Action, page 9, 1rst ¶).

Applicants strongly dispute the Examiners comments that it is a "trivial undertaking" to formulate inhaled compounds. Perhaps the Examiner should look closely at the compound covered by the claims of the '055 patent, tiotropium. Of the 5 patents, and 2 reissues listed in the Orange Book for Tiotropium, this one is not present.

There are however, multiple patents and claims directed to tiotropium based upon other crystalline forms, salt forms, micronisates, and generic formulas, such as in US 7,309,707:

1. Crystalline tiotropium bromide micronisate, characterised by a particle size X_{50} of between 1.6 μm and 3.5 μm or a $Q_{6.4}$ value of more than 60%, by a specific surface value in the range between 2 m^2/g and 5 m^2/g, by a specific heat of solution of more than 68 W·s/g and by a water content from about 1% to about 4.5%, wherein the crystalline tiotropium bromide micronisate is obtained from crystalline tiotropium bromide monohydrate, which crystalline tiotropium bromide monohydrate when thermally analysed by DSC has an endothermic maximum at 230±5° C. at a heating rate of 10K/min, has an IR spectrum which has bands inter alia at wavelengths 3570, 3410, 3105, 1730, 1260, 1035 and 720 cm^{-1} and which is characterised by a single monoclinic cell with the following dimensions: a=18.0774 Å, b=11.9713 Å, c=9.9321 Å, β=102.691°, V=2098.66 Å³.

Crystalline forms in US 6,777,423:

1. Crystalline tiotropium bromide monohydrate having an endothermic peak at 230° C.±5° C. occurring during thermal analysis using DSC at a heating rate of 10 K/min.

Anhydrous crystalline forms in the cited US 6,608,055 patent:

1. Anhydrous crystalline tiotropium bromide.

2. Anhydrous crystalline tiotropium bromide according to claim 1, having a monoclinic crystal system wherein a monoclinic elementary cell has the parameters a=10.4336(2) Å, b=18.3293(3) Å, c=17.6333(4) Å, α=90°, β=108.1582)° and γ=90° (cell volume=2013.86(8) Å³) as determined by X-ray structural analysis.

Or there are multiple patents and claims directed to tiotropium having particular particle sizes, fractional amounts in the formulation, varying particle size of the actual mixtures, etc., such as described in US 7,070,800:

1. An inhalable powder comprising 0.04 to 0.8% of tiotropium in admixture with a physiologically acceptable excipient, wherein the excipient consists of a mixture of coarser excipient with an average particle size of 15 to 80 μm and finer excipient with an average particle size of 1 to 9 μm, the proportion of the finer excipient constituting 1 to 20% of the total amount of excipient, wherein the inhalable proportion of active substance is released reproducibly in low variability amounts when administered to a patent.

2. An inhalable powder according to claim 1, wherein the tiotropium is present in the form of the chloride, bromide, iodide, methanesulphonate, para-toluenesulphonate or methyl sulphate thereof.

3. An inhalable powder comprising between 0.048 and 0.96% of tiotropium bromide in admixture with a physiologically acceptable excipient, wherein the excipient consists of a mixture of coarser excipient with an average particle size of 15 to 80 μm and finer excipient with an average particle size of 1 to 9 μm, the proportion of the finer excipient constituting 1 to 20% of the total amount of excipient, wherein the inhalable proportion of active substance is released reproducibly in low variability amounts when administered to a patent.

4. An inhalable powder comprising between 0.05 and 1% of tiotropium bromide monohydrate in admixture with a physiologically acceptable excipient, wherein the excipient consists of a mixture of coarser excipient with an average particle size of 15 to 80 μm and finer excipient with an average particle size of 1 to 9 μm, the proportion of the finer excipient constituting 1 to 20% of the total amount of excipient, wherein the inhalable proportion of active substance is released reproducibly in low variability amounts when administered to a patent.

5. An inhalable powder according to one of claims 1, 2, 3 or 4, wherein the excipient consists of a mixture of coarser excipient with an average particle size of 17 to 50 μm and finer excipient with an average particle size of 2 to 3 μm. ;

Tiotropium in micronized forms, as shown in US 5,478,578:

1. Powder for inhalation comprising a micronized active substance and a physiologically acceptable excipient comprising a mixture containing a fine fraction having an average particle size in the range of less than 10 μm and a coarse fraction having an average particle size in the range of from about 20 μm to about 150 μm, wherein the weight ratio of micronized active substance to the physiologically acceptable excipient mixture is from about 0.01:5 to 0.1:5.

It would be therefore be clear to the skilled artisan upon review of the multiple patents and applications filed for the compound in question, e.g. one which has hydrates, solvates, and various crystalline forms, that formulation of such is not a "trivial undertaking" as so alleged by the Examiner.

The compounds of the present invention are not 3-oxa-9-azoniatricyclo [3.3.1.0] derivatives, nor do then have an ester linkage off the nonane bridged ring. Such characteristics may produce compounds which have differing requirements to the instantly claimed compounds herein.

The Examiner has not provided any motivation to direct the skilled artisan to make a pharmaceutical formulation of the compounds of Zirkle as a dry powder inhalable formulation absent Applicants own disclosure. The '478 patent and the Med Chem. Articles of Zirkle do not teach nor suggest a pharmaceutical formulation, let

alone use of the compounds for anticholinergic activity via the inhaled route of administration. The teachings of Gillett et al. provide no disclosure or teaching which would direct the skilled artisan to formulate the presently claimed compounds for use as an inhaled compound, and the teaching of Sieger et al. are directed to a crystalline anhydrous form of an unrelated chemical compound. Consequently, the Examiner and the USPTO have failed to make out a *prima facie* case of obvious.

In view of these remarks, reconsideration and withdrawal of the rejection to the claims under 35 USC §103 over Zirkle et al. is respectfully requested.

Rejection under 35 USC § 112

Claims 1 to 4 and 6 to 16 are rejected under 35 USC § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Examiner cites the various In re Wands factors and specifically comments that the "claims are broad and drawn to many conditions, respiratory and otherwise but that's not really the main concern here, the main concern it's that these compound have not been shown to be useful for treating any disease." (Office Action, page 11, Point (A)).

The Examiner's comments on Applicants past arguments on these point is simply that "While the Applicant has provided no actual information, but only prophetic assays, the Examiner will maintain the enablement rejection for the reasons of record".

This is clearly incorrect.

"The enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003), citing *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). Clearly, one of ordinary skill in the art would be able to synthesize a wide range of compounds of Formula (I) which are within the scope of the genus. This has been satisfied by the USPTO's allowance of the compounds of Formula (I) in US 2,800,478.

The specification also provides details on what the compounds are useful for, e.g. treatment of respiratory-tract disorders (page 1 to page 4, lines 1 to 4; page 5, lines 15 to 30 to page 9, lines 1 to 19. These compound's as enunciated by the Examiner in

the rejection under 35USC § 103 clearly "disclose the pharmacological activity of these compounds, namely that they inhibit acetylcholine induced response with activity similar to atropine". (See Office Action, line 1, page 4). See also Office Action, page 8, last ¶ where "Regardless, since the compounds of the instant case are anticholinergics …" it would be obvious to … test them as anticholinergics". (See Office Action, line 1, page 9. The Examiner has conceded that the compounds as claimed herein are muscarinic antagonists. There is no unpredictability in the art as to their intended usage based upon the Examiner's own logic.

Applicant's invention is the novel use of these compounds as a composition for delivery to the lungs, whether it is via the oral inhalation route or nasal delivery. The application provides a significant discussion on the various inhalers and formulation details therein. Consequently, it is believed that one of ordinary skill in the art is provided with sufficient information to also be able to use the compounds of Formula (I).

As noted, there may not even be a requirement to have <u>any</u> working embodiments in order to satisfy the requirements of § 112, first paragraph, even in the chemical arts, as evidenced by the decision in *In re Strahilevitz*, 668 F.2d 1229, 212 U.S.P.Q. 561 (CCPA 1982). In this case, Applicants had described the invention with specificity, but had not disclosed even a single operative embodiment. The court acknowledged that the claims at issue were extremely broad, yet the court reversed the Board's holding of nonenablement, having been persuaded by Strahilevitz that the invention consisted in combining known prior art techniques. Pointing out that § 112 does not require working examples (though they may be desirable in complex technologies), the court found the broad claims enabled throughout their scope. In *Strahilevitz*, Applicants were able to obtain broad claims to methods for removing haptens from blood, despite the fact that no working examples were disclosed, because the evidence of record established that the prior art had taught methods that, when combined together according to the teachings of the specification, could be used to make the claimed invention.

The MPEP 2164.01(c) on How to Use the Claimed Invention also clearly contemplates that a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, and that 25 USC §112 is thereby satisfied.

The state of the art, taken with Applicants specification is sufficient within the context of M3 receptors antagonists to be enabled.

By law a patent application is presumptively enabled when filed. That is, during examination, "[a]s a matter of Patent Office practice . . . a specification . . . must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d at 223, 169 U.S.P.Q. at 369.

Moreover,

> . . . it is incumbent upon the Patent Office, whenever a rejection on [grounds of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Id. at 224, 169 U.S.P.Q. at 369-70.

Since the PTO bears the initial burden of challenging the presumed utility of an invention, it must produce sufficient evidence that one of ordinary skill in the art would have reason to doubt the claimed utility of the invention.

One of skill in the art, in combination with the submitted references as well as the state of the art would not question the claimed utility of the compounds described and claimed herein. The nature of the applicants' invention itself would also not tend to cause one skilled in the art to doubt its usefulness. In fact, the very compounds cited by the Examiner in the Office Action, Tiotropium is a muscarinic acetylcholine antagonist.

As regards Applicants claimed subject matter, Claim 6 is a recitation that the composition (of Claim 1) inhibit the binding of acetylcholine to an acetylcholine receptor in a mammal. This method is not tied to the treatment of a particular disease state or respiratory condition as so noted by the Examiner, and is well supported in the specification. The second binding assay, page 6, lines 16 to 24 provides for a pan muscarinic antagonism screening against the M1 to M5 acetylcholine receptors. None of the commercially available compounds are 100% selective for any one of the

muscarinic receptors, where antagonism of the M3 receptor is most desired for inhaled compounds. The skilled artisan would readily understand the significance of this assay and the potential limitations of compounds tested therein. This is a well known art recognized assay. The method of claim 6 does not require" treatment of a disease state". The claim limitations in Claim 6 are such that a compound of Formula (I) contact a particular receptor and that this contact is made by a route of administration, e.g. inhalation for receptors in the respiratory tract.

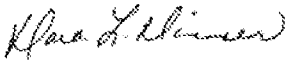
The specification provides for formulation details, amounts, how to use. And how to administer the claimed dry powder formulations of compounds of Formula (I), and reference additional patents on the various devices for such formulations.

In view of these remarks, reconsideration and withdrawal of the rejection to the claims is respectfully requested.

CONCLUSION

It is believed that the claims, as amended, are now all in condition for allowance. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. It is not believed that this paper should cause any additional fees or charges to be required, other than expressly provided for already. However, if this is not the case, the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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